

WHAT IS CLAIMED IS:

1. A method of sequencing a population of polynucleotides encoding antibodies or T-cell receptors, the method comprising:

- (a) contacting a plurality of oligonucleotides of known sequences, at least a portion of said plurality of oligonucleotides having a partial sequence similarity, with the population of polynucleotides under conditions allowing a formation of hybridization duplexes between at least a portion of said plurality of oligonucleotides and said population of polynucleotides;
- (b) quantitatively detecting oligonucleotides involved in said formation of said hybridization duplexes; and
- (c) compiling a set of sequences of the population of polynucleotides by:
 - (i) identifying oligonucleotides involved in said formation of said hybridization duplexes in a quantum above a predetermined threshold, so as to define a population of positively hybridizing oligonucleotides;
 - (ii) identifying germline sequences of germline segments in at least a portion of said positively hybridizing oligonucleotides or in at least a portion of said oligonucleotides involved in said formation of said hybridization complexes;
 - (iii) identifying positively hybridizing oligonucleotides overlapping with said germline sequences, thereby identifying germline junction sequences; and
 - (iv) assembling sequence information obtained from steps (ii) and (iii), thereby compiling said set of sequences of the population of polynucleotides;

thereby sequencing the population of polynucleotides encoding the antibodies or T-cell receptors.

2. The method of claim 1, wherein step (ii) further comprises identifying oligonucleotides of non-redundant germline sequences in said germline segment.

3. The method of claim 1, wherein each oligonucleotide of said at least a portion of said plurality of oligonucleotides is selected to hybridize with a known germline segment and an unknown sequence.

4. The method of claim 1, wherein said plurality of oligonucleotides are collectively selected to hybridize with all germline segments of the population of polynucleotides.

5. The method of claim 1, wherein said plurality of oligonucleotides is selected to non-redundantly hybridize with said germline segments of the population of polynucleotides.

6. The method of claim 1, wherein the population of polynucleotides comprise RNA molecules.

7. The method of claim 1, wherein the population of polynucleotides comprise DNA molecules.

8. The method of claim 1, the method further comprising, prior to step (a), amplifying selected segments of said polynucleotides encoding the antibodies or the T-cell receptors, said selected segments encoding variable regions of the antibodies or the T cell receptors.

9. The method of claim 8, wherein said variable regions comprise variable regions of heavy chains of antibodies.

10. The method of claim 8, wherein said variable regions comprise variable regions of light chains of antibodies.

11. A method of quantifying an expression of a population of polynucleotides encoding antibodies or T-cell receptors, the method comprising:

- (a) contacting a plurality of oligonucleotides of known sequences, at least a portion of said plurality of oligonucleotides having a partial sequence similarity, with the population of polynucleotides under conditions allowing a formation of hybridization duplexes between at least a portion of said plurality of oligonucleotides and said population of polynucleotides;
- (b) quantitatively detecting oligonucleotides involved in said formation of said hybridization duplexes; and
- (c) compiling a set of sequences of the population of polynucleotides by:
 - (i) identifying oligonucleotides involved in said formation of said hybridization duplexes in a quantum above a predetermined threshold, so as to define a population of positively hybridizing oligonucleotides;
 - (ii) identifying germline sequences of germline segments in at least a portion of said positively hybridizing oligonucleotides or in at least a portion of said oligonucleotides involved in said formation of said hybridization complexes;
 - (iii) identifying positively hybridizing oligonucleotides overlapping with said germline sequences, thereby identifying germline junction sequences;
 - (iv) assembling sequence information obtained from steps (ii) and (iii), thereby compiling said set of sequences of the population of polynucleotides, and
- (d) determining a level of each set of said compiled set of sequences of step (iv) in said population of polynucleotides, thereby quantifying the expression of the population of polynucleotides encoding the antibodies or T-cell receptors.

12. The method of claim 11, wherein step (ii) further comprises identifying oligonucleotides of non-redundant germline sequences in said germline segment.

13. The method of claim 11, wherein each oligonucleotide of said at least a portion of said plurality of oligonucleotides is selected to hybridize with a known germline segment and an unknown sequence.

14. The method of claim 11, wherein said plurality of oligonucleotides are collectively selected to hybridize with all germline segments of the population of polynucleotides.

15. The method of claim 11, wherein the population of polynucleotides comprise RNA molecules.

16. The method of claim 11, wherein the population of polynucleotides comprise DNA molecules.

17. The method of claim 11, the method further comprising, prior to step (a), amplifying selected segments of said polynucleotides encoding the antibodies or the T-cell receptors, said selected segments encoding variable regions of the antibodies or the T cell receptors.

18. The method of claim 17, wherein said variable regions comprise variable regions of heavy chains of antibodies.

19. The method of claim 17, wherein said variable regions comprise variable regions of light chains of antibodies.

20. An oligonucleotide library for sequencing by hybridization of polynucleotides encoding variable regions of antibodies or T cell receptors, the library consisting essentially of:

(i) a set of overlapping oligonucleotides collectively selected to hybridize with all germline segments encoding the variable regions of the antibodies or T cell receptors under conditions allowing formation of

hybridization duplexes between said set of overlapping oligonucleotides and said polynucleotides; and

- (ii) a variant set of oligonucleotides of said overlapping oligonucleotides which comprises (G,C,T,A) base variation in at least one position of said overlapping oligonucleotides;

wherein oligonucleotides of said sets of overlapping oligonucleotides and said variant set of oligonucleotides are N bases in length and said overlapping is of at least N-(N-1) and whereas N is an integer equal or greater than 5.